DEPARTMENT OF H .LTH & HUMAN SERVICES
Public Health Service

FOOD & DRUG ADMINISTRATION
466 FERNANDEZ JUNCOS AVENUE
SAN JUAN, P.R. 00901-3223
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June 29, 1998

WARNING LETTER
SJN-98-14

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Mr. Francisco R. Rodriguez
General Manager
Schering-Plough Products, Inc.
P. O. Box K-1779
Las Piedras, Puerto Rico 00771-1779

Dear Mr. Rodriguez:

During an inspection of your manufacturing facility located in Las Piedras, Puerto Rico conducted from March 18 through May 7, 1998, our investigators documented deviations from the Current Good Manufacturing Practice Regulations (Title 21, Code of Federal Regulations, Parts 210 and 211) and the requirements for NDA Field Alert Reporting (Title 21, Code of Federal Regulations, Part 314.81). These deviations cause Theo-Dur Extended Release Tablets to be adulterated within the meaning of Section 501(a)(2)(B) of the Food Drug and Cosmetic Act (Act) in that the controls used for the manufacturing, processing, packing, or holding do not conform with current good manufacturing practice regulations and other regulations promulgated under the Act.

1. Extension of the expiration period beyond the 24 months approved for Theo-Dur Extended Release Tablets.

   Records show that your firm's procedures allow for assignment of expiration periods based on the date blending and/or lubrication occur, instead of the initial date of manufacturing. Your procedures are also unclear as to how the initial date of manufacturing is to be determined for the finished drug product. Based on your current practice, the active coated pellets, the waxed pellet, and final coat intermediates used in Theo-Dur can each be stored for up to six months before they are used in the process. This holding period, which could extend for up to 18 months, is not taken into account when assigning an expiration period for finished products. [21 CFR 211.137(a) and 211.166(a)]

   This is a recurrent deficiency previously documented for Theo-Dur Sprinkle Capsules during an inspection made of your firm during October 1994.

2. Failure to conduct in-process testing of all lots of intermediate materials used in the manufacturing process of Theo-Dur Extended Release Tablets. [21 CFR 211.160(b)(2)]

Records show that your firm reduced the testing of your active coating solution, final coated pellets, and other intermediates to one in 20 lots since 1991.

ANDA 85-328 for Theo-Dur ER Tablets includes in-process specifications for the active solution, active coated, wax coated and final coated pellets; however, these in-process tests are only being done to one in every 20 lots of intermediates.

3. Failure to submit, within three working days, an FDA Field Alert Report (FAR) for Theo-Dur 300 mg. Extended Release Tablets lot 01617364 (packaging lot 96867), which failed to meet the 6 and 8 hour NDA dissolution specifications at the 12 month stability test station. [21 CFR 314.81(b)(1)]

   Your firm submitted your initial FAR for this lot on 9/15/97, after your investigation had been completed; however, records reviewed show this lot failed S1 dissolution on 8/17/97. Dissolution S2 & S3 testing done on 8/20/97 and 8/24/97, respectively, confirmed the failing result.

4. Also, we are concerned about your solution to address the variability in absorbance during testing of Claritin 10 mg tablets by recording the maximum at only 280 nm. The question still remains as to why the maximum of the standard solution and samples changes so drastically within the same run. Your firm should conduct a full investigation to assess the cause of the problem.

We acknowledge your firm's response, dated May 18, 1998, to the Form FD-483 (List of Inspectional Observations) presented at the conclusion of the inspection on May 7, 1998. Our evaluation of this response finds that except for the issues mentioned in this letter, including those listed above which relate to observations # 17, 18 & 26, the corrective actions proposed in your response should, when properly implemented, adequately address the remainder of the deviations listed on the FD-483.

The above identification of violations is not intended to be an all inclusive list of deficiencies at your facility. It is your responsibility to assure all requirements under the Food Drug and Cosmetic Act and the regulations promulgated thereunder are being met. Federal agencies are advised of the issuance of all Warning Letters about drugs so that they can take this information into account when considering the award of contracts. Additionally, pending NDA, ANDA, or export approval requests may not be approved until the above violations are corrected.

You should take prompt measures to correct these deviations. Failure to promptly correct these deviations may result in regulatory action without further notice. Such action include seizure and/or injunction.

Please notify this office in writing within 15 working days of receipt of this letter, of the specific steps you have taken to correct the noted violations and to prevent their recurrence. If corrective action cannot be completed within 15 working days, state the reason for the delay and the time within which the corrections will be completed. Where applicable, include copies of any available documentation demonstrating that corrections have been made.

Your reply should be sent to the Food and Drug Administration, San Juan District Office, San Juan, Puerto Rico 00901-3223, Attention: Maridalia Torres, Acting Compliance Officer.

Yours Truly,

Samuel Jones
District Director